UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,866	02/01/2001	David Thomas	PNJ-001	3286

7590 07/12/2005

DARBY & DARBY
ATTN: PAUL F. FEHLNER, PH.D
805 THIRD AVE.
NEW YORK, NY 10022

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/773,866	THOMAS ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-24,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/27/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

9.00

DETAILED ACTION

1. Applicant's amendment, filed 4/27/05, has been entered.
Claims 25-28 have been canceled. Claims 1-20 have been canceled previously.
Claims 21-22 have been amended.

Claims 21-24 and 29-30 are pending and being acted upon as they read on applicant's election of Species A (anti-CD40 antibody).

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendment, filed 4/27/05.
The rejections of record can be found in previous Office Action, mailed 12/28/04.

3. The drawings, filed 4/27/05, are accepted by the examiner.

4. Claims 21-24 and 29-30 are rejected under 35 U.S.C.§ 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:
"for enhancing a pre-existing immune response",
"contacting" and/or
"without completely blocking".

Applicant's amendment, filed 4/27/05, asserts that no new matter has been added and directs support to page 2, lines 9-12; pages 16-17 and Examples 4-5 on pages 22-23 of the instant specification for the written description for the above-mentioned "limitations".

However, the specification as filed does not provide sufficient written description as to the "above-mentioned limitations". None of these "above-mentioned limitations" appears in the specification as directed and neither does the context of the specification as these referenced sections of the instant specification provide sufficient blazemarks or direction for the instant methods encompassing the above-mentioned "limitations", as currently recited.

For example, the citation on page 2 of the specification describes activation of T helper cells by dendritic cells resulting in the upregulation of CD40L, not "for enhancing a pre-existing immune response".
Further, pages 16-17 of the specification are drawn to in vitro culture assays, including generating dendritic cells with anti-CD40 antibodies in the induction of T lymphocytes, not "for enhancing a pre-existing immune response", "contacting" and/or "without completely blocking", ", as currently recited.
In addition, Examples 4-5 on pages 22-23 of the specification may describe partial blocking of CD40L by up to 88%, but not provide sufficient written description for "without completely blocking", as currently recited.

The instant claims now recite "limitations" which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the Alimitations≅ indicated above. See MPEP 714.02 and 2163.06.

5. Claims 21-24 and 29-30 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments, filed 4/27/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant merely asserts that the claims have been amended to recite "enhancing a pre-existing immune response and "contacting an antibody", but does not address the objective evidence of record, reiterated herein for applicant's convenience.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vitro experimental observations on the binding of anti-CD40 antibodies accurately reflects the relative efficacy of the claimed therapeutic strategy to induce antigen specific cytotoxic T cell responses by administering agonistic anti-CD40 antibodies in the absence of antigen.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

The specification does not adequately teach how to induce antigen specific cytotoxic T lymphocyte responses in the absence of administering an antigen. For example, Melief et al. (US 2003/0022860) describe Experiments which show that CD40-triggering can prime cytotoxic T cell responses in vivo (see paragraph [0045]. To this end, mice were injected with E1A/IFA vaccine in combination with the activating anti-CD40 antibody. Mice that received this combination mounted strong E1A-specific CTL response, whereas mice that received the E1A/IFA vaccine or antibody alone did not. The specification does not teach how to extrapolate data obtained from in vitro binding inhibition assays to the development of effective in vivo therapeutic methods that can induce antigen specific T lymphocytes in the absence of a specific antigen. Therefore, it is not clear that the skilled artisan could predict the efficacy of inducing an antigen specific cytotoxic lymphocytes by administering anti-CD40 antibody in the absence of an antigen.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, making and using anti-CD40 antibodies in the absence of antigen would provide the antigen-specific cytotoxic T cell response encompassed by the claimed methods would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant's arguments have not been found persuasive.

5. Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 contains the trademark or trade name "DeImmunized9" Where a trademark or trade name is used in a claims as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph, See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark or the trade name "DeImmunised™" is used to identify or describe a product or possibly a product-by-process, and accordingly, the identification or the description is indefinite. The relationship between a trademark or tradename and the product it identifies may be uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or tradename.

Applicant's arguments, filed 4/27/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that "DeImmunised™" is not a product, but "a method of treating antibodies" (?).

However, as page 8, paragraph 1 of the instant specification discloses:
"DeImmunised™ antibodies are antibodies in which the potential T cell epitopes have been eliminated as, described in International Patent Application PCT/GB98/01473."

Therefore, the specification acknowledges that "DeImmunised™ antibodies are antibodies", that is "DeImmunised™ antibodies are products, not methods.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

6. Claims 21-24 and 30 are rejected under 35 U.S.C. § 102 (e) as being anticipated by Melief et al. (US 2003/0022860 A1; Jan. 30, 2003) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 4/27/05, have been fully considered but are not found convincing essentially for the reasons of record and those addressed herein.

Applicant argues that Melief et al. does not teach each and every element of the claims since it does not disclose "without blocking binding of CD40L to CD40" and "enhancing pre-existing immunity".

As pointed out previously, Melief et al. teach methods of treating tumors or infectious diseases comprising administering anti-CD40 antibodies or fragments thereof, including monoclonal, chimeric, humanized, human, DEIMMUNISED and single chain antibodies (see paragraphs [0029] – [0034] and a CTL activating peptide by generating or enhancing immune responses via the CD40 pathway on dendritic cells. (see Background of the Invention, Summary of the Invention, and Making and Using the Invention). Methods of administration by injection are described (see paragraph [0036]).

In response to applicant's arguments, the described methods of treating tumors or infectious diseases are targeting patients with "pre-existing immunity".
Also, it is noted that Example 4 of Melief et al. indicating that strength of the anti-tumor response is enhanced when presented by activated dendritic cells, indicating enhancing preexisting immunity in vaccinated individuals.

Further, it is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.
Therefore, the prior art teaching of administering agonistic antibodies with antigen or in methods of vaccination are encompassed by the broadest reasonable interpretation of the instant methods.

Melief et al. employs the activating anti-CD40 antibody FGK-45 (see paragraph [[0045]). Although the reference is silent about the claimed recitation of "without blocking binding of CD40L to CD40", it appears that Melief et al. teach agonistic anti-CD40 antibodies, including the specific FGK-45 specificity. Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons. The burden is on the applicant to establish a patentable distinction between the claimed and referenced agonistic anti-CD40 antibodies.

Applicant has not provided objective evidence to obviate the prior art teaching of agonistic anti-CD40 antibodies that read on the instant agonistic antibodies.

For example, Examples 1 – 2 of Melief et al. teach that signaling through CD40 can replace $CD4^+$ helper T cells in CTL priming and that the defect in CTL-priming induced by CD40L blockade lies in the failure of TH cells to transmit, rather than to receive CD40L-mediated signals.

Therefore, the referenced agonistic CD40-specific antibodies do not appear to operate via CD40:CD40L epitopes, thus meeting the claimed limitations, in the absence of objective evidence to the contrary.

Further, it is noted that the prior art and the instant application appear to have a common assignee, so applicant appears to be in the best position to address this issue.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods of stimulating immune responses to tumors and infectious diseases with agonistic anti-CD40 antibodies and a CTL activating peptide. Unlike the current claims, the prior art teaches the provision of a CTL activating peptide, which, in turn, induced a specific CTL mediated immunity.

Applicant's arguments have not been found persuasive.

7. Claims 21-24 and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Melief et al. (US 2003/0022860 A1; Jan. 30, 2003) in view of Zhou et al. (Hybridoma 18: 471 - 478, 1999) (of record) AND/OR Caux et al. (Research in Immunology 145: 235-239, 1994) (of record) AND/OR Katira et al. (Leukocyte Typing V, Schlossman et al. (Ed.), Oxford University Press, Oxford 1995, page 554) (of record) AND/OR Schwabe et al. (Hybridoma 16 : 217 – 226, 1997) (of record)) essentially for the reasons of record.

Claim 29 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Melief et al. (US 2003/0022860 A1; Jan. 30, 2003) in view of Zhou et al. (Hybridoma 18: 471 - 478, 1999) AND/OR Caux et al. (Research in Immunology 145: 235-239, 1994) AND/OR Katira et al. (Leukocyte Typing V, Schlossman et al. (Ed.), Oxford University Press, Oxford 1995, page 554) AND/OR Schwabe et al. (Hybridoma 16 : 217 – 226, 1997)
as applied to claims 21- 24 and 30 above and further in view of Maraskovsky et al. (U.S. Patent No. 6,497,876)) essentially for the reasons of record.

Applicant's arguments, filed 4/27/05, have been fully considered but are not found convincing essentially for the reasons of record and those addressed herein.

Applicant's arguments and the examiner's rebuttal are essentially the same as those addressed above in the previous Section 6.

Further, once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather merely asserts that the prior art does not provide sufficient suggestion or motivation to enhance immune responses with agonistic antibodies and does not address the teachings of the references individually and not their teachings individually or in combination.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In addition, the arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01 (C). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

In this case, the following is reiterated for applicant's convenience.

Melief et al. teach methods of treating tumors or infectious diseases comprising administering anti-CD40 antibodies or fragments thereof, including monoclonal, chimeric, humanized, human, DEIMMUNISED and single chain antibodies (see paragraphs [0029] – [0034] and a CTL activating peptide by generating or enhancing immune responses via the CD40 pathway on dendritic cells. (see Background of the Invention, Summary of the Invention, and Making and Using the Invention). Methods of administration by injection are described (see paragraph [0036]).

Melief et al. employs the activating anti-CD40 antibody FGK-45 (see paragraph [[0045]). Although the reference is silent about the claimed recitation of "without blocking binding of CD40L to CD40", it appears that Melief et al. teach agonistic anti-CD40 antibodies, including the specific FGK-45 specificity. Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons. The burden is on the applicant to establish a patentable distinction between the claimed and referenced agonistic anti-CD40 antibodies.

In addition, the following references Zhou et al., Caux et al., Katria et al. and Schwabe et al. all teach that a number of agonistic anti-CD40 antibodies were known and employed by the ordinary artisan at the time the invention was made. Furthermore, these references teach that such agonistic anti-CD40 antibodies encompass stimulatory anti-CD40 antibodies that block and do not block CD40 : CD40L interactions.

For example, Zhou et al. teach the agonistic anti-human CD40 antibody 5C11, which triggers the generation, proliferation and maturation of dendritic cells from peripheral blood monocytes (see entire document, including the Abstract).

For example in a Workshop on a panel of anti-CD40 antibodies, Katira et al. identify various epitopes on CD40, including the existence of several functional epitopes that support the presence of more than one ligand for this important receptor (see entire document on page 554).

Schwabe et al. teach the characterization of anti-CD40 antibodies, which also supports the presence of various epitopes, not all of which rely upon the CD40L binding region, as recognized by agonistic anti-CD40 antibodies. Further, Schwabe teach that the mimetic effects binding of the CD40L epitope was not of advantage (see Abstract). Schwabe et al. teach the advantages of multiple epitopes in regulating immune interactions and responses (see Discussion).

Given the number of anti-CD40 antibodies at the time the invention was made, it would have been obvious to the ordinary artisan at the time the invention was made to employ (e.g. administer, inject) agonistic anti-CD40 antibodies, including those that inhibit CD40L binding and those that do not inhibit CD40L binding to CD40 to stimulate the desired antigen-specific immune responses directed toward antigens associated with treating tumor or infectious diseases, as taught by Melief et al. at the time the invention was made. The claimed functional limitations would be intrinsic or expected properties of the referenced methods of stimulating immune responses to tumors and infectious diseases with agonistic anti-CD40 antibodies, including those agonistic antibodies that do not inhibit CD40:CD40L interactions, as taught by the secondary references, and a CTL activating peptide. Unlike the current claims, the prior art teaches the provision of a CTL activating peptide, which, in turn, induced a specific CTL mediated immunity.

It was well known to use of chimeric, humanized, DeImmunized, human antibodies as well as antibody fragments at the time the invention was made, as acknowledged by Melief et al. In addition to the decreased immunogenicity of recombinant antibodies and antibody fragments, the use of the claimed antibodies and antibodies fragments were all well known and practiced at the time the invention in a wide variety of assays and methods, including detection and therapeutic modalities.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With respect to the rejection "further in view of Maraskovsky et al. (U.S. Patent No. 6,497,876), the following is reiterated for applicant's convenience.

Melief et al. in view of Zhou et al., Caux et al., Katira et al. and Schwabe et al. differ from the claimed methods by not disclosing the well known use of interferon- γ to treat patients with tumors and infections in combination therapy.

Maraskovsky et al. teach the well known use of interferon-γ to treat patients with tumors and infections, including the administration of such cytokines as interferon- γ in combination therapy (e.g. see column 2, paragraph 2 and Preparation of Antigens on columns 10-11). It is noted that the teachings of Maraskovsky et al. are directed to the use of stimulating antigen specific dendritic cells via stimulating the CD40:CD40L pathway, which in turn, provides further motivation and expectation of success of combining interferon- γ with modalties that rely upon stimulating CD40 pathways in the generation of antigen-specific immune responses to antigens (e.g. tumor- / infection-related antigens).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Maraskovsky et al. to those of combination of references which stand for the administration of agonistic CD40 antibodies, including those that do not bind the CD40L binding epitope on CD40, to obtain combination therapies combining the administration of both agonistic anti-CD40 antibodies and interferon- γ. According to references, a person of ordinary skill in the art would have been motivated to combine both agonistic anti-CD40 antibodies and interferon- γ to generate antigen-specific CTL responses to antigens of interest, since both reagents were able to increase such immune response and combination was known and practiced at the time the invention was made, as evidence by Maraskovsky et al.

Applicant's arguments have not been found persuasive.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PHILLIP GAMBEL

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
July 6, 2005